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Annals of Oncology 28 (Supplement 8): viii8–viii12, 2017
doi:10.1093/annonc/mdx445

SYMPOSIUM ARTICLE

The new classifications of ovarian, fallopian tube, and primary peritoneal cancer and their clinical implications

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The roles of histologic characterization and staging are to provide reproducible metrics for cancer classification with which to direct the most appropriate clinical care and to yield the most stable reliable system to allow both prospective and retrospective data analysis. Both the histologic and staging classifications of malignant ovarian/tubal/peritoneal cancers have recently changed. The World Health Organization sponsored a review and reclassification of the pathology of cancers of the ovaries, fallopian tubes, and peritoneum, and published these updates in 2014. In so doing, they codified the two-tiered grading system that has been in use in serous ovarian cancers for nearly a decade. In parallel, FIGO reviewed and updated the surgical staging system, applied to all histotypes of ovarian, tubal, and peritoneal cancers, also published in 2014. In both cases, the changes made are meant to encompass a better understanding of disease, but both have important merits and drawbacks. Changes in staging complicate analysis of retrospective data against current data. Though in some aspects controversial, the changes overall are meant to represent a better biologic understanding of disease that we hope will lead to an improvement in patient care and directed therapy.

Key words: Ovarian cancer, staging, FIGO, WHO

Out with the old and in with the new

Both the histologic and staging classifications of malignant ovarian/tubal/peritoneal cancers have recently changed. Change is often embraced because it is perceived to be progress, growth, or success. Creating such change to yield better biologic understanding of disease that then leads to an improvement in patient care and directed therapy, is one of the primary goals of scientific investigation. However, change can also bring about controversy. The World Health Organization (WHO) sponsored a review and reclassification of the pathology of cancers of the ovaries, fallopian tubes, and peritoneum, and published these updates in 2014 [1–4]. In parallel, the International Federation of Gynecology and Obstetrics (FIGO) reviewed and updated the surgical staging system, applied to all histotypes of ovarian, tubal, and peritoneal cancers, also published in 2014 [5, 6]. In both cases, the changes made are meant to encompass a better understanding of malignant tubo-ovarian disease, but both have important pitfalls that must be acknowledged and addressed.

The purposes of histologic classification, grading, and staging of cancers are manifold (Table 1). They are predominantly patient-oriented and related to provision of reproducible metrics for classification of cancers to direct clinical care through diagnostic accuracy, prognostication, and treatment planning. Reliable, reproducible, accurate classification systems are also important tools for cross evaluation of demographic, epidemiologic, treatment, and outcomes data, through which to understand historic outcomes and to provide a platform from which to analyze future findings. Thus, the most consistent, simple to use, and long-standing system provides the most stability and reliability for patient care planning and data analysis. Herein lie the controversies.

Table 1. Roles of staging and grading

- To describe the characteristics of the cancer architecture and cells
- To provide reproducible metrics to be used within a tumor and across tumors
- To describe and organize reproducible tumor characteristics that correlate with prognosis
- To inform and organize treatment recommendations
- To provide a platform from which to understand and dissect historical information
- To provide a platform from which to build, direct, and analyze prospective clinical advances.

The WHO histotype classification changes of 2014

The new WHO classification is in line with what is generally being done in patient care and, with its relative simplicity, allows retrospective classification rather readily so older 'data' are not 'lost'. The histologic differences between the five major types of epithelial ovarian cancer can be identified even by the nongynecologic pathologist. Overall, the WHO classification codifies what has been in use in many countries for a decade or more, with a few additional twists. It incorporates many major scientific advances in our understanding of epithelial cancers of the ovary, fallopian tubes, and peritoneum. It recognizes probable precursor events, lineages, and molecular characteristics. The major changes are summarized in Table 2 and further discussed below.

Serous cancers are now divided by low and high grade in a simpler system, readily determined by architecture, potential involvement of a serous borderline component, lack of diffuse p53 immunostaining and/or mutation, and frequent *BRAF/KRAS* mutations. Micropapillary serous borderline variant is recognized for its higher risk of peritoneal implants, within which there is a 50% probability of serous low-grade cancer at its base. How a moderately well-differentiated or grade 2 tumor should be classified has been addressed with more clarity. Such cancers should undergo p53 immunostaining and if positive should be considered high grade [7]. The frequency of *p53* loss of function mutations in high-grade serous ovarian cancer (HGSOC) appears to range around 33% and can be determined by complete absence of p53 within the tumor, whereas lack of *p53* mutation should be associated with sporadic tumor cell nuclear p53 staining [8]. High-grade cancers of serous/endometrioid/transitional histology now come together under the HGSOC label, with common *p53* mutation. The role of the precursor, such as endometriosis and serous tubal intraepithelial carcinoma (STIC) lesion is mentioned, but not fully integrated into reclassification of 'ovarian' cancers, for example, in a stage 0 or TIS designation. No significant changes were proposed for ovarian clear cell cancer, despite its frequent association with and transformation from underlying endometriosis [9, 10]. The codification of change that is in place in many institutions worldwide makes more clear the distinctions of the different types of ovarian/fallopian tube/peritoneal cancers and will allow more clear harmonization of data and understanding of disease.

There is value to the recognition that a proportion of micropapillary borderline tumors will actually be true grade 1 carcinomas, and there will be clinical consequences to the proposed change in nomenclature. Currently, micropapillary borderline tumors are treated with surgery alone, and not with adjuvant chemotherapy [11]. With the new classification, it is possible that patients with micropapillary borderline tumors who previously would have not received adjuvant chemotherapy, may likely be offered adjuvant treatment. It is unclear how or if to reconsider treatment planning within this new system. Low-grade serous cancers do not respond to chemotherapy as robustly as do their high-grade relatives [12, 13]. Whether there is better initial therapy requires well-constructed clinical trials and the willingness of the oncologic community to risk a radical change in primary therapy, generally considered the only curative therapeutic opportunity.

The requirement for p53 testing for grade 2 tumors will appropriately re-classify a percentage of grade 2 tumors to high grade. However, there will be no clinical implications for this change, since currently grade 2 and 3 carcinomas are treated in the same manner. In contrast, the re-classification of tumors into low and high grade is likely to result in some grade 2 serous tumors being reclassified as low-grade serous cancer. Care will need to be taken to collect data on how these patients respond, their demographics, and the biologic characterization of their tumors in order to further support this reclassification and to determine whether there may be subsets of low-grade serous cancers with different prognoses.

The WHO classification fails to recognize the importance of precursor lesions for tumor types other than HGSOCs. They have embraced the role and importance of STIC, the precursor for the high-grade tubal lesions. However, the persistent classification of clear cell cancer as of ovarian origin, despite the evidence for its origin from endometriosis, is one that is worthy of further investigation and could have clinical implications [14, 15]. For example, while the safety of hormone replacement in ovarian cancer has been established, there have been inadequate numbers

Table 2. Major changes in WHO classification and supporting reasons

Major changes	Supporting reasons
Formal adoption of the two-step grading system	Supported by science
Papillary cystic BOT → SBOT/ atypical proliferating tumor	Cystic serous tumor with >10% BOT is now SBOT
Papillary surface BOT → SBOT, micropapillary type, noninvasive LGSOC	High risk of peritoneal implants (27 versus 13%) for micropapillary; 50% probability LGSOC in peritoneal SBOT base
'Grade 2' tumors are candidates for p53 immunostaining	Likely HGSOC, support by p53 staining
Endocervical MBOT → seromucinous	Resembles SBOTs with one-third associated with endometriosis and *ARID1a*^{mut}

BOT, borderline ovarian tumor; MBOT, mucinous borderline ovarian tumor; SBOT, serous borderline ovarian tumor; HGSOC, high-grade serous ovarian carcinoma; LGSOC, low-grade serous ovarian carcinoma.

Table 3. Molecular characteristics associated with epithelial ovarian cancer histologies

Type	% of total	Molecular characteristics	Other notes
HGSOC	70	*TP53*^{mut}, genomic instability	STIC precursor, no BOT
LGSOC	3.5	*KRAS*^{mut}, *BRAF*^{mut}	Mutations more common in SBOT
CCC	10	*ARID1a*^{mut}, *PIK3CA*^{mut}, *PIK3CA*^{amp}	15%–30% with endometriosis
ENDO lgr	10	*ARID1a*^{mut}, *PIK3CA*^{mut}, *PTEN* LOH, *ß catenin*^{mut}	EBOT frequency of mutations similar to invasive, 15%–30% associated with endometriosis
ENDO hgr		*TP53*^{mut}	Recategorized as HGSOC
Mucinous	3.6	80%$^{+}$ *KRAS*^{mut}	Intestinal type only

lgr, low grade; hgr, high grade.

Table 4. Major FIGO staging changes and supporting reasons

Major changes	Supporting reasons
Designate histologic site	Scientifically supported, no longer lumps fallopian tube with ovary
Stage III now Any LN+ any spread beyond pelvis IIIA1 is LN+ only IIIA2 micro-disease+LN+	Retrospectively ∼10% IIIA are LN+ behave like I/II; LGSOC can arise in nodal endosalpingiosis
Stage IV^{+} effusion versus parenchyma/inguinal/other nonabdominal nodal sites	Retrospective data → differential outcome for effusion-only stage IV

LN, lymph node.

of women with nonserous histologies in those studies and retrospective case series. Thus, it is unclear that traditional hormone replacement exposure is safe for women with clear cell cancer that arose from endometriosis, especially if they have residual endometriosis. Endometriosis implants remaining after debulking surgery may be stimulated by unopposed estrogen therapy and the effects of such hormone on their malignant potential is as yet unknown.

The new WHO classification also focuses on the controversies in mucinous cancer. It emphasizes considering metastasis rather than primary disease in all cases of mucinous ovarian tumors, including mucinous borderline tumors. This is an important distinction as biologically it is likely that a large percentage of these mucinous tumors are metastases from other primary sites, and a full investigation for the true primary tumor is warranted and could change patient care. However, the new classification does not have clinical implications for those tumors that are determined to be likely primary from the ovary. The new category of seromucinous cancer may be confusing to clinicians who do not recognize their more malignant potential or the probable susceptibility to standard chemotherapy.

Finally, the new WHO classification does not incorporate molecular characteristics into the new classification. As the scientific community moves forward in the era of precision medicine, these molecular characteristics could become critical in making treatment decisions. Testing for germline deleterious mutations in *BRCA1* or *BRCA2* is done routinely in many countries in the world and is the only validated true predictive biomarker for ovarian cancers. This information has not yet been demonstrated to affect primary patient care, but has led to new and different treatment recommendations for women with recurrent disease. Similar value for other molecular findings has not been demonstrated. Many molecular findings have prognostic value but are not yet proven to drive treatment decisions (Table 3). Changes may be recommended for incorporation as the field continues to mature.

The FIGO staging reclassification changes of 2014

The major changes in the FIGO 2014 staging reclassification are summarized in Table 4 and further discussed below. The FIGO 2014 staging reclassification raises more questions, especially related to the role of staging to provision of reproducible metrics as a platform for harmonization of historic and future results.

First, the FIGO staging system is not selective to epithelial ovarian/tubal/peritoneal cancers, but includes stromal and germ cell tumors of the ovary as well. It is unclear if this system is optimal for those nonepithelial cancers for the staging goal of driving patient care and prognostication. However, even within the epithelial cancers, it is presented as a one-size-fits-all classification. Second, most of the changes were made on only or nearly only retrospective case series of epithelial cancers. Such outcomes can be viewed with skepticism because of the great dependence upon the skill and aggressiveness (or not) of the debulking surgeon, limited information based upon the extent of surgery and the quality of the pathology review, and the selection bias that cannot be avoided in retrospective studies. Issues arise, such as: was there no lymphadenectomy because the patient may have already been considered stage IIIC (FIGO 1988) and felt not to have a benefit/risk balance for further surgery, or because the patient was felt to be a stage I, albeit without an adequate upper abdomen or lymph node assessment. Third is the ongoing controversy regarding stage 2 disease, and whether, as with the two-level grading system, there should be a three-level staging system, local/advanced/metastatic. This would obviate having to explain the conjecture

that the pelvis is identified by an invisible line between anterior iliac crests, and local can be more consistently defined. The issue of pleural effusion can again be wrapped into metastatic disease so that the positive pleural biopsies of the aggressive surgeons that now upstage patients to stage IVB will no longer be an issue, and not contribute to stage variability. Last, and concerning, is the issue for data harmonization. These changes were made in a fashion that makes retrospective re-grading difficult and causes stage shifting; any lymph node positive is now IIIA whereas those patients were IIIC previously, causing stage down-migration. Therefore, there can be no comparison of clinical trial outcomes where the staging system differs, FIGO 1988 versus FIGO 2014. That change nullifies over two decades of clinical trials and clinical progress, including many of the seminal studies of intraperitoneal therapy, taxane schedule studies, and more and makes risky the use of prior outcomes for powering new studies.

Despite these concerns, there is value to the new FIGO system. The formal recognition of STIC as a precursor lesion for serous ovarian cancers is important. The creation of a new staging category for lymph node only positive disease acknowledges that this disease distribution has a better prognosis than stage 3 disease on the basis of peritoneal dissemination [16]. However, the system also has pitfalls. In particular, the new system fails to recognize and account for the growing trend across the world to use neoadjuvant chemotherapy. In some centers and countries, 50% or more of patients are being treated with neoadjvuant chemotherapy [17, 18]. Many of these patients have a 'clinical' stage assigned before treatment, based upon examination and imaging. This is a nonvalidated approach and it remains unclear how this clinical staging will affect data harmonization and evaluation going forward. There is also a building trend to use minimally invasive surgery at the time of interval debulking surgery [19]. Whether this approach will give the same surgical completeness for an R0 designation and depth of evaluation for 'interval staging' as is seen with open primary or open interval surgery is unknown. Lymph nodes are less likely to be removed in women who have been treated with neoadjuvant therapy and therefore these data will be lost in the staging system. The recognition that neoadjuvant therapy is being used more frequently suggests the need for a staging system that accommodates these patients and allows us to be able to interpret data regarding prognosis and best treatment.

Discussion

The advances provided by the WHO epithelial ovarian/tubal/peritoneal cancer histologic classification are notable. It is a more simple and supportable system that incorporates histology and cytology, and invites use of time-honored and validated molecular classifications where questions arise. It can be applied retrospectively where tissue resources (slides, photomicrographs, etc.) exist so adds value without losing history. In contrast, the FIGO 2014 staging reclassification, done with the best of intentions, changes the landscape in a less transparent and harmonious way and needs to be applied and considered with caution. It also needs added sections for 'clinical' staging and/or 'interval' staging for women receiving neoadjuvant chemotherapy.

Many of the FIGO changes were based on data from retrospective studies. These studies are confounded by their retrospective nature, the aggressiveness of the surgical practice from which they were reported, the specific nature of the reported population (lack of racial and socioeconomic diversity), and the significant but unrecognized bias that only those patients who are well enough to undergo extensive debulking surgery are included in the report. In other words, the FIGO changes based on these data are potentially not generalizable. Stage is determined by surgical findings, but not all surgeries, and not all patients, are created equal. An aggressive surgeon may be willing to completely cytoreduce (including lymph node dissection, upper abdomen disease extirpation) a young, motivated, insured patient, although the same might not apply to a patient who is older, sick, has lack of access to care, or is not treated at a tertiary institution. Additionally, the new system does not account for those patients who are treated with neoadjuvant chemotherapy, a proportion of whom might never get to the operating room.

Second, the new system adds staging complexity that provides no associated clinical implications. The sub-setting of stage 2 disease is a great example, since all patients with stage 2 disease will receive chemotherapy, and the majority of clinical trials of 'advanced' disease are choosing to include patients with stage 2 disease, recognizing that these women belong in that high-risk category. The subset of stage IIIA is also scientifically and clinically irrelevant.

Third, the FIGO system includes germ cell and stromal ovarian tumors with the epithelial tumors; from a clinical standpoint, this is not reasonable. It is time for FIGO to acknowledge the significant differences between these tumor types and create a separate staging system for these tumors. Since many germ cell tumors will occur in young women and children, it makes sense for FIGO to work with pediatric oncology groups to develop a joint staging system that will be clinically useful regardless of patient age. There should be harmonization across juvenile and young adult tumors with respect to surgical management and chemotherapy recommendations.

Finally, we have amassed a trove of data based on current FIGO staging that is a valuable resource and comparator as we move forward scientifically in the treatment of women with ovarian cancer. Does it make sense to change the staging system now, making comparison to older studies more difficult if not impossible?

Change is embraced because it is perceived to be progress, especially when it is data-driven and based on science. The changes in the WHO and FIGO classifications need to be understood and critically evaluated in that context, as we move forward in a better understanding and improved care of women with cancers of the ovary, fallopian tube and peritoneum.

Funding

The publication of this supplement and the symposium on which it is based have been supported through partnership between the Spanish Ovarian Cancer Research Group (GEICO) and the European Society for Medical Oncology (ESMO).

Disclosure

The authors have declared no conflicts of interest.

References

1. Kurman RJ, Carcangiu ML, Herrington CS. WHO Classification of Tumors of the Female Reproductive Organs. Lyon: WHO Press, 2014.
2. Meinhold-Heerlein I, Fotopoulou C, Harter P et al. The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet 2016; 293: 695–700.
3. Meinhold-Heerlein I, Fotopoulou C, Harter P et al. Erratum to: the new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet 2016; 293: 1367.
4. Meinhold-Heerlein I, Fotopoulou C, Harter P et al. Statement by the Kommission Ovar of the AGO: the new FIGO and WHO classifications of ovarian, fallopian tube and primary peritoneal cancer. Geburtshilfe Frauenheilkd 2015; 75: 1021–1027.
5. Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014; 124: 1–5.
6. Zeppernick F, Meinhold-Heerlein I. The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. Arch Gynecol Obstet 2014; 290: 839–842.
7. Vang R, Shih Ie M, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol 2009; 16: 267–282.
8. Salani R, Kurman RJ, Giuntoli R II et al. Assessment of TP53 mutation using purified tissue samples of ovarian serous carcinomas reveals a higher mutation rate than previously reported and does not correlate with drug resistance. Int J Gynecol Cancer 2008; 18: 487–491.
9. Prowse AH, Manek S, Varma R et al. Molecular genetic evidence that endometriosis is a precursor of ovarian cancer. Int J Cancer 2006; 119: 556–562.
10. Wiegand KC, Shah SP, Al-Agha OM et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 2010; 363: 1532–1543.
11. Park JY, Kim DY, Kim JH et al. Micropapillary pattern in serous borderline ovarian tumors: does it matter? Gynecol Oncol 2011; 123: 511–516.
12. Santillan A, Kim YW, Zahurak ML et al. Differences of chemoresistance assay between invasive micropapillary/low-grade serous ovarian carcinoma and high-grade serous ovarian carcinoma. Int J Gynecol Cancer 2007; 17: 601–606.
13. Schmeler KM, Sun CC, Bodurka DC et al. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 2008; 108: 510–514.
14. Munksgaard PS, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. Gynecol Oncol 2012; 124: 164–169.
15. Anglesio MS, Papadopoulos N, Ayhan A et al. Cancer-associated mutations in endometriosis without cancer. N Engl J Med 2017; 376: 1835–1848.
16. Berek JS. Lymph node-positive stage IIIC ovarian cancer: a separate entity? Int J Gynecol Cancer 2009; 19(Suppl 2): S18–S20.
17. Barber EL, Dusetzina SB, Stitzenberg KB et al. Variation in neoadjuvant chemotherapy utilization for epithelial ovarian cancer at high volume hospitals in the United States and associated survival. Gynecol Oncol 2017; 145: 500–507.
18. Karam A, Ledermann JA, Kim JW et al. Fifth ovarian cancer consensus conference of the Gynecologic Cancer InterGroup: first-line interventions. Ann Oncol 2017; 28: 711–717.
19. Gueli Alletti S, Bottoni C, Fanfani F et al. Minimally invasive interval debulking surgery in ovarian neoplasm (MISSION trial-NCT02324595): a feasibility study. Am J Obstet Gynecol 2016; 214: 503.e1–503.e6.